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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/194,889	08/23/1999	LILI FENG	TSRI540.1	3717

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EXAMINER	
SAOUD, CHRISTINE J	
ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 12/26/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/194,889	FENG et al.
Examiner	**Art Unit**
Christine Saoud	1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Oct 20, 2000*.

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 6, 7, 18-31, and 33* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 6, 7, 18-31, and 33* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *12*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Claims 4-5, 8-17, 32, 34 and 35 have been canceled and claims 18 and 27 have been amended as requested in the amendment of paper #11.5, filed 23 October 2000. Claims 1-3, 6-7, 18-31 and 33 are pending in the instant application.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed 23 October 2000 have been fully considered but they are not deemed to be persuasive.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-3 and 6-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled

in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims are directed to a method of treating a patient having a condition in which regulating energy metabolism during a systemic inflammatory response is desired by administering a physiologically effective amount of at least one OB-R agonist ligand. However, it would appear that stimulation of the OB receptor by an agonist would be contrary to the treatment of a patient with such a condition. As evidenced by Grunfeld et al. (European Cytokine Network. 7(2): 258, 1996), factors which are released during inflammation induce leptin mRNA and circulating levels of leptin correspond to those levels of inflammatory cytokines. During infection, the host experiences anorexia, which appears to be mediated by the inflammatory cytokines' effects on leptin (or OB) expression and circulating plasma levels. Therefore, during infection and a "systemic inflammatory response" it would appear that the regulation of energy metabolism is such that one would want to stimulate weight gain, and not decrease it. Therefore, the administration of an OB-receptor agonist would be contrary to what would be considered a treatment, and the claims are not enabled.

As this rejection is based on the interpretation of "regulating energy metabolism", the claim is also indefinite because it is not clear how the energy metabolism is to be regulated and therefore, it is not clear what physiological effect is to be mediated (see 112/2nd rejection below). If Applicant clarifies these phrases, the prior art of Grunfeld et al. may be reapplied because Grunfeld et al. suggest that it is the leptin (or OB) which mediates the anorexia of infection,

therefore, if anorexia is the desired effect, the administration of exogenous OB would be *prima facie* obvious to one of ordinary skill in the art.

7. Claims 18, 20-24 and 27 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record in paper #11.

Applicant argues at page 5 of the response that "compounds including cytokines are well known to one of ordinary skill in the art and that such a person would consider the invention reasonably to include any molecule that is known or could readily be evaluated with the methods of the invention" and that "determination of a compound having the requisite activity is not undue". This argument is not persuasive because enablement of the claimed invention requires that one of ordinary skill in the art be able to practice the claimed method without undue experimentation. As the claims encompass all agents which regulate expression of the Ob-R, the claims encompass such things as antisense, ribozymes, and other expression regulatory agents, which are not predictive one form the other. Regulation of gene expression is unpredictable, administration of antisense and gene therapy is unpredictable, the instant specification provides no guidance for such methods of using these kinds of agents, and it would require a substantial inventive contribution by the skilled artisan to practice the method as it is broadly claimed. Applicant argues that one could perform an assay to ascertain appropriate inducers for use, but this argument is akin to a "wish to know" for those agents which could be used in the claimed

method and would require the skilled artisan not only to identify which agents may have potential in the claimed method, but also require the skilled artisan to develop the experimental protocol for the method to be function, which clearly demonstrates that the specification contains subject matter which was not described in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as it is currently claimed.

With regard to claim 27, Applicant argues that the claim as written is enabled. This argument is not persuasive. The instant specification fails to provide a single example of the treatment of a patient by administration of IL-6 and OB protein. Furthermore, as there are a multitude of conditions in which OB protein has been implicated, one of ordinary skill in the art at the time the instant invention would not reasonably expect the administration of the set amounts of IL-6 and OB protein recited in the instant claim to be effective for treatment of all such conditions. Different disease states and conditions which are associated with OB, and reduced OB receptor, are not regulated in the same manner, and therefore, would not be expected to be treated in the same manner. For example, as a condition characterized by OB resistance in which the defect is at the level of the receptor, the administration of OB or an agent which induces OB expression would be useless because no amount of OB is going to make up for the defective receptor. As the instant specification fails to provide a single example of treatment of a patient, the unpredictability of the art with regard to mechanisms of disease, the lack of guidance in the specification and the prior art regarding the claimed invention, it would require undue

experimentation of one of ordinary skill in the art to practice the invention as claimed, absent evidence to the contrary.

8. Claims 1-3, 6-7, 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3 and 6-7 are directed to methods of treating a patient having a condition in which "regulating energy metabolism during systemic inflammatory response is desired" by administering a "physiologically effective amount" of an OB-R agonist. However, as the claim fails to indicate how the energy metabolism is to be regulated, one cannot determine what would be a "physiologically effective amount". The metes and bounds of "physiologically effective amount" cannot be determined from the claim and therefore, the claims are indefinite.

Claim 18 recites "therapeutic cytokine OB-R expression inducer". This phrase does not appear to find support in the instant specification as filed, therefore, the metes and bounds of such cannot be determined. It would appear that Applicant wishes to limit the OB-R expression inducer agent to cytokines, however, this could be done by rewording the claim to administration of a cytokine which induces OB-R expression.

9. Claim 33 recites the limitation "the sample" in line 3 of the claim. There is insufficient antecedent basis for this limitation in the claim. As there is no recitation of where "the sample" is to be taken, and it fails to refer back to the patient, there is insufficient antecedent basis for this element.

10. Claim 33 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: are steps that correlate detection of binding of antibody to OB with some inflammatory response. The method steps fail to achieve the goals of the method as presence of OB does not provide for an assay for inflammatory response as OB is present under normal conditions as well as under disease conditions. Therefore, the method appears to be lacking method steps and is incomplete.

Claim Rejections - 35 USC § 102/103

11. Claim 33 stands rejected under 35 U.S.C. 102(b) as being anticipated by, or in the alternative, under 103(a) as being obvious over Friedman et al. for the reasons of record in paper #11.

Applicant argues that Friedman fails to teach use of an OB antibody in assaying a disease marker for an inflammatory response. Applicant should note the 112/2nd rejection of the instant claim above. As Friedman et al. meets all of the method steps of the claim, Friedman et al. also anticipates the claim. If Applicant amends the instant claim to overcome the 112/2nd rejection made above, Friedman et al. may no longer be prior art, but this is dependent on any future claim amendments.

12. Claims 18-26, 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grunfeld et al. (J. Clin. Invest. 97(9): 2152-2157, 1996).

Grunfeld et al. disclose that endotoxins and cytokines (related to inflammation and infection) induce expression of leptin/OB in response to infection. It is the expression of leptin/OB and the resultant secretion of leptin/OB which is determined to contribute to the anorexia of infection. Based on these findings, one of ordinary skill in the art at the time of the instant invention would readily ascertain that the OB is beneficial to the anorexic response and that the inflammatory endotoxins and cytokines enhance this response by inducing expression of endogenous OB, and therefore, the co-administration of the two compounds would be useful for treating conditions requiring anorexia, or weight loss. Therefore, treatment of a patient with obesity with an OB-receptor agonist, such as OB, and an agent which induces expression of OB, such as LPS, TNF, IL-1, IL-6, and INF, would have been prima facie obvious in light of the teachings of Grunfeld et al., absent evidence to the contrary. One would be motivated to use the combination of agents because the administration an agent which induces expression of OB would enhance the anorexic response and would increase the patient's own system to treat the obesity.

Applicant argues that Grunfeld fail to disclose the administration of OB and an endotoxin or a cytokine in combination. In so far as this argument addresses the 102 rejection, this argument is persuasive and is why the claims are no longer rejected as anticipated by the reference.

Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Christine J. Saoud, Ph.D., whose telephone number is (703) 305-7519. The Examiner can normally be reached on Monday to Friday from 7AM to 3PM. If attempts to reach

the Examiner by telephone are unsuccessful, the Examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623.

Certain papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1 (CM1). The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. §§ 1.6(d) and 1.8). NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers.

Official papers filed by fax should be directed to (703) 872-9306. If this number is out of service, please call the Group receptionist for an alternate number. Official papers filed After Final rejection filed by fax should be directed to (703) 872-9307.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

December 21, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud